REMARKS

Claims 46, 54-77, and 80-107 are pending in the present application. Independent claims 46 and 76 have been amended to recite "wherein the medicament is in solid particle form." Support for these amendments may be found throughout the specification as filed, e.g., at page 5, line 5 to line 19.

The Invention

Until recently, chlorofluorocarbons (CFCs) were widely used as propellants in pressurized metered dose inhalers (pMDI) for delivery of medicaments to the airways. CFCs are organic compounds. Where the medicament to be delivered by pMDI was not soluble in organic media such as liquefied CFC, it was typically formulated as a suspension of fine powder particles in the liquefied propellant. Surfactants were commonly included in order to aid dispersion of the medicament particles in the CFC propellant; without such surfactants, the particles would tend to aggregate. According to page 97, col.1, lines 19-23, of McDonald et al., International Journal of Pharmaceutics 201:89-107, 2001 (attached as Appendix A), the surfactants used with "currently licensed" CFC metered dose inhalers are oleic acid, sorbitan triethanoleate and soya derived lecithin.

Due to environmental concerns, CFCs are now being replaced by a new generation of propellants: hydrofluoroalkane (HFA) propellants. As explained in the present application as well as in McDonald et al., *supra*, and Williams et al., Eur. J. Pharm. Biopharm. 48:131-140 (1999) (attached as Appendix B), the surfactants commonly used with CFC formulations are not necessarily suitable for use with HFAs. Applicants have found that certain classes of surfactants are particularly suitable for dispersing fine particles of medicament in the new generation of propellant. The present claims (as amended) are drawn to formulations containing an HFA, a medicament in solid particle form, and an alkyl saccharide surfactant, and methods of using such formulations in therapy.

Provisional Obviousness-Type Double Patenting

Claims 46, 54-58, 61-77, 80, 82, 83, and 96-101 were provisionally rejected for obviousness-type double patenting over claims 1, 10-41, 48-62, 74-105, and 114-127 of U.S. Pat. No. 6,524,557. Applicants will file an appropriate terminal disclaimer once the claims are otherwise deemed allowable.

35 USC §103(a)

All of the claims were rejected as obvious over WO 91/11495 in view of Neale et al., Sequeira et al., and Meezan et al. According to the Examiner,

> The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of fluorocarbons, medicine and alkyl saccharides in a pharmaceutical aerosol formulation. However, the prior art amply suggests the same as it is known to produce pharmaceutical aerosols containing fluorocarbons and surfactants and that alkyl saccharides are suitable for use as surfactants in medical aerosols. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that the medical aerosol would exhibit increased bioavailability of the administered medicine(s) and would be suitable for administration of a broader range of medicines.

Applicants respectfully traverse.

The pending claims are limited to formulations (and methods of use thereof) comprising HFAs, medicaments, and a specific class of surfactants: alkyl saccharides. WO 91/11495, Neale et al., and Sequeira et al. all disclose various formulations containing HFAs, medicaments, and surfactants generally; as recognized by the Examiner, none of the surfactants is an alkyl saccharide. To be more specific, WO 91/11495 discloses the use as a surfactant of (1) an ester of a polyalcohol, perhaps a sorbitan ester with higher saturated or unsaturated fatty acids, e.g., sorbitan trioleate; or (2) a polyethoxysorbitan ester of a higher, preferably unsaturated fatty acid; or (3) a phospholipid, possibly a lecithin.

Neale et al. discloses the use of fluorocarbon propellants with a laundry list of surfactants: oleic acid, sorbitan trioleate (Span®85), sorbitan mono-oleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan mono-oleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, synthetic

lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl mono-oleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, cetyl pyridinium chloride, benzalkonium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil and sunflower seed oil).

Sequeira et al. simply generally discloses the use of HFC-134A or HFC-227 "with or without surfactants," with no further discussion of what those surfactants should be. To reiterate, none of these surfactants is, or is related to, an alkyl saccharide.

Thus, as recognized by the Examiner, none of WO 91/11495, Neale et al., or Sequeira et al., alone or in combination, discloses that the surfactant can be an alkyl saccharide, as required by the present claims.

Meezan et al. is cited to make up for this deficiency. Meezan is the only reference cited that mentions alkyl saccharides at all (termed "alkyl glycosides" in Meezan). One of skill in the art would not have been motivated to combine the teachings of WO 91/11495, Neale et al., or Sequeira et al., which disclose nothing more than the use of non-aqueous organic hydrofluorocarbon propellants with certain surfactants (but not alkyl saccharides), with the teachings of Meezan et al., which discloses aqueous formulations of medicaments and alkyl saccharide surfactants (the formulations utilized in Meezan's examples are formulated in saline). One of skill in the art would appreciate that medicaments formulated in an aqueous solution and medicaments formulated in a non-aqueous, organic medium would behave very differently, as they have very different chemical and physical properties.

As discussed in McDonald et al. (Appendix A) at page 97, even if a given surfactant has been proven to be useful with the non-aqueous medium CFC, one can't assume it will also be useful with the non-aqueous medium HFA, as their physical and chemical properties are different. As McDonald notes, hydrofluoroalkanes are more polar than CFCs and have different solvency properties (see p. 97). However, CFCs and HFAs are far more similar to each other than HFAs are to water. For example, the dispersion forces, polar forces, and hydrogen bonding forces at play in an aqueous solution, especially saline, differ from those in HFAs such as 1,2-difluoroethane (HFC152), 1,1-difluoroethane (HFC152a), 1,1,2-trifluoroethane (HFC143), 1,1,1-trifluoroethane (HFC143a), 1,1,1,2-tetrafluoroethane (HFC134a), and 1,1,2,2-tetrafluoroethane (HFC134), and slight disparities in polar contributions result in considerable differences in

solubility behavior. As is further made clear in Williams et al. (Appendix B), solubility in water and in HFA can be completely different, and addition of other agents may have opposite effects on solubility in HFA and in water (see p. 137, esp. Table 4).

For the foregoing reasons, one of skill in the art would have had no motivation to combine the references as suggested by the Examiner. "To prevent the use of hindsight based on the invention to defeat patentability of the invention, [Federal Circuit law] requires the Examiner to show a motivation to combine the references that create the case of obviousness. In other words, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner cited." *In re Rouffet,* 149 F.3d 1350 (Fed. Cir. 1998). No such showing has been made.

There must be a teaching or suggestion, within the prior art or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534 (Fed. Cir. 1998). Before the Applicants had the insight to use alkyl saccharides as a surfactant with HFAs, there was neither any teaching nor any suggestion in the art to use such a combination, and given the differences discussed herein between the HFA compositions of the invention and the aqueous solutions of Meezan, there would have been no reasonable expectation of success. The Examiner has used impermissible hindsight to pick and choose references to combine, based solely on the Applicants' invention.

Even though the Applicants believe the claims to be allowable as previously written, the Applicants have amended independent claims 46 and 76 to facilitate prosecution of this application. The claims as amended are drawn to pharmaceutical aerosol formulations comprising a hydrofluoroalkane (HFA) propellant; a physiologically effective amount of a medicament for inhalation; and an alkyl saccharide surfactant, wherein the medicament is in solid particle form. This amendment makes abundantly clear that the teachings of Meezan et al., which, as discussed above, relate to aqueous formulations, have no relevance for the claimed invention.

For the foregoing reasons, the claimed invention is not obvious over any combination of WO 91/11495, Neale et al., Sequeira et al. and/or Meezan et al., and withdrawal of the rejection under 35 U.S.C. § 103(a) is hereby respectfully requested.

Applicants respectfully request consideration of all previously filed Information Disclosure Statements, with each item on all Form 1449s initialed, specifically, the Information Disclosure Statement/Form 1449 filed by the Applicants on December 19, 2002. Applicants further request a copy of such initialed Form 1449. Furthermore, Applicants bring to the Examiner's attention the following applications and patents, all of which are assigned of record to the assignee of the present application and have overlapping inventorship:

U.S. Patent No. 5,506,203
U.S. Patent No. 5,518,998
U.S. Patent No. 5,658,878
U.S. Patent No. 5,747,445
U.S. Patent No. 5,830,853
U.S. Patent No. 5,952,008
U.S. Patent No. 6,004,574
U.S. Patent No. 6,165,976
U.S. Patent No. 6,306,440
U.S. Patent No. 6,436,902
U.S. Application Serial No. 08/601,005
U.S. Application Serial No. 09/665,585
U.S. Application Serial No. 10/401,157
U.S. Application Serial No. 10/224,522

Enclosed is a check for $410.00 for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account No. 06-1050, referencing attorney docket number 06275-034001.

Respectfully submitted,

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